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Prospective Randomized Trial of Early Postoperative Intraperitoneal Chemotherapy as an Adjuvant to Resectable Gastric Cancer

Wansik Yu, MD,* Ilwoo Whang, MD,* Insoo Suh, MD,† Andrew Averbach, MD,‡ David Chang, MS,§ and Paul H. Sugarbaker, MD‡

From the Department of Surgery, Kyungpook National University, Taegu, Korea, the Department of Pathology,† Kyungpook National University, Taegu, Korea, The Washington Cancer Institute, Washington, DC,‡ and Westat, Rockville, Maryland§*

Objective

Surgeons have postulated on numerous occasions that cancer resection may participate in the dissemination of a malignancy. This randomized trial sought to determine whether a large volume of chemotherapy solution used perioperatively to flood the peritoneal cavity could eliminate microscopic residual disease and thereby improve survival of patients with gastric cancer.

Summary Background Data

Surgical treatment failures in patients with gastric cancer are confined to the abdomen in most patients. Resection site and peritoneal surface spread, along with liver metastases, are the most common areas of recurrence. Survival and quality of life of patients with gastric cancer would be improved if disease progression at these anatomic sites was reduced.

Methods

In a prospective randomized trial of 248 patients, intraperitoneal mitomycin C on day 1 and intraperitoneal 5-fluorouracil on days 2 through 5 were administered after gastric cancer resection. Patients who were thought to have stage II or stage III disease were randomized after resection to surgery alone *versus* surgery plus early postoperative intraperitoneal chemotherapy. After final pathologic examinations, there were 39 patients with stage I, 50 with stage II, 95 with stage III, and 64 with resected stage IV cancer.

Results

The 5-year survival of the surgery-only group was 29.3%, and the surgery-plus-intraperitoneal chemotherapy group was 38.7% ($p = 0.219$). In a subset analysis, the patients with stage I, stage II, and stage IV disease showed no statistically significant difference in survival. The 5-year survival rate of patients with stage III disease who underwent surgery only was 18.4% *versus* a survival rate of 49.1% for patients who underwent surgery plus intraperitoneal chemotherapy ($p = 0.011$).

Conclusions

In a subset analysis, patients with stage III gastric cancer have shown a statistically significant improvement in survival when treated with perioperative intraperitoneal chemotherapy. Further studies in patients with gastric cancer with surgically directed chemotherapy are suggested.

The long-term results of treatment for resectable gastric cancer have not shown any significant improvement in recent decades.[1] Considerable efforts were made to develop adjuvant therapies, but large randomized trials of intravenous chemotherapy or radiotherapy failed to demonstrate improved survival.[2–4] Wanebo and colleagues[5] did not report any beneficial trend from multimodality therapy.

Analyses of recurrence patterns after curative resection have shown that local and intraabdominal disease had an impact on survival in that they were the only sites of the first recurrence in approximately 50% of patients. Even at death,

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Address correspondence and reprint requests to Paul H. Sugarbaker, MD, The Washington Cancer Institute, 110 Irving Street, NW, Washington, DC 20010.
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the tumor often remained confined to the abdomen.[6–8] Anatomic sites of treatment failure with postoperative adjuvant treatments and neoadjuvant chemotherapy were essentially the same as after surgery alone.[9,10] After extended lymphadenectomy, the peritoneal surfaces and the liver remained major sites of recurrence. However, the rate of locoregional relapse was considerably lower when compared with more limited surgery.[11–13]

From this analysis of data on surgical treatment failure, intraperitoneal chemotherapy as an adjuvant to surgery may be considered a rational therapeutic modality. Also, the results of published randomized trials of adjuvant perioperative intraperitoneal chemotherapy demonstrated a trend, or significant improvement, in survival compared with surgery alone.[14–17] In a single study in which intraperitoneal chemotherapy followed surgery by several weeks no difference was noted.[18] It has been suggested that not only the route (intraperitoneal *vs.* intravenous) but also the timing (perioperative *vs.* delayed) of this surgically directed chemotherapy administration was crucial to the benefits reported in these trials.[19–21]

Within the context of surgical technology, this adjuvant intraperitoneal chemotherapy trial was designed to investigate the possibility that surgery participated in the dissemination of gastric cancer cells into the resection site and onto peritoneal surfaces. Viable gastric cancer cells repeatedly have been identified within the peritoneal cavity after gastrectomy.[22,23] These cancer cells are presumed to be released from transected lymphatic channels or from tissue at narrow margins of resection. Another possible source is tumor-contaminated blood lost in the surgical field from the cancer specimen.[19,20] Perioperative intraperitoneal chemotherapy can be used to flood the entire abdominal and pelvic cavity including the gastric cancer resection site with a large volume of fluid containing a cancericidal drug dose. Because the treatments are initiated before adhesions occur in a large volume of fluid, distribution is nearly uniform. Will this treatment be able to eliminate microscopic residual disease traumatically disseminated at the time of surgery? If the trial was positive, it must enhance the concept of the surgeon as part of the iatrogenic dissemination of gastric cancer.[24–28]

PATIENTS AND METHODS

From January 1990 to December 1995, 248 patients with biopsy-proven gastric cancer without distant metastases according to preoperative routine staging (physical examination, chest x-ray, computed tomography scan, or ultrasound of the abdomen) and intraoperative staging were enrolled in the study. Patients older than 70 years of age and those who were thought, by endoscopy, to have stage I disease were excluded. All patients underwent surgery at Kyungpook National University Hospital in Taegu, Korea. Patients were randomized intraoperatively after resection was complete to receive early postoperative intraperitoneal mitomycin C on postoperative day 1 and 5-fluorouracil on days 2 through 5 *versus* surgery alone. Tumors of the 248 randomized patients were determined to be resectable by the responsible surgeon's judgment. Other exclusion criteria were prior antitumor therapy or prior malignancy except for basal cell carcinoma of the skin or carcinoma-*in-situ* of the cervix, and pregnancy. Eligible patients had a white blood cell count of at least 4000/mcl or more, a platelet count 150,000/mcl or more, a blood urea nitrogen level of less than 30 mg/dl, and a creatinine concentration less than 1.5 mg/dl. All patients signed an informed consent form that explained the investigational nature of the study.

Surgery

All of the patients had their surgery performed in Taegu, Korea. Depending on location and macroscopic type of gastric cancer, either total or distal subtotal gastrectomy was selected. All patients underwent extended lymphadenectomy, and the resected specimen was studied according to the Japanese Classification of Gastric Carcinoma.[29] The extent of lymph node dissection was selected at the discretion of a surgeon according to his clinical judgment regarding the extent of disease. Routine Roux-en-Y reconstruction with stapled esophagojejunostomy or hand-sewn Bilroth-II gastrojejunostomy was used. In patients randomized to receive early postoperative intraperitoneal chemotherapy, a Tenckhoff catheter (Quinton, Seattle, WA) and two closed-suction drains were placed into the peritoneal cavity before the abdomen was closed.[30]

Early Postoperative Intraperitoneal Chemotherapy

On the day of the surgery after completion of gastrectomy, the peritoneal cavity was irrigated with 1.5% dextrose peritoneal dialysis solution until drainage from the catheters became clear. On the first postoperative day, 1 liter of 1.5% dextrose dialysis solution containing 10 mg/m^2 of mitomycin C warmed to 37°C in a dry incubator was instilled as rapidly as possible into the peritoneal cavity via a Tenckhoff catheter. The catheter and drains were clamped for 23 hours. During the first 6 hours of treatment with mitomycin C, a urine output of greater than 1 ml/kg body weight/hour was maintained. On day 2, the peritoneal cavity was drained for 1 hour, and 700 mg/m^2 of 5-fluorouracil plus 50 mEq of sodium bicarbonate in 1 liter of 1.5% dextrose dialysis solution were instilled. The 5-fluorouracil instillations were repeated daily for a total of four treatments. Initially, the Tenckhoff catheter and drains were removed on the sixth postoperative day. Later in the course of the study, to more completely remove intraperitoneal fluid, the drains were left in place until drainage subsided.

Table 1. CHARACTERISTICS OF PATIENTS TREATED WITH SURGERY PLUS EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY (EPIC) OR SURGERY ONLY

Characteristics	Surgery & EPIC	Surgery Alone	p value
Total no. of patients	125	123	
Male:Female	84:41	81:42	0.822
Mean age ± SD	53.9 ± 9.6	55.0 ± 9.9	0.389
Mean of follow-up in months (range)	31.2 (1.3–72.9)	26.3 (0.7–63.7)	
Location: Proximal (%)	17 (13.6)	20 (16.3)	
Body (%)	48 (38.4)	24 (19.5)	
Distal (%)	55 (44.0)	69 (56.1)	
All stomach (%)	5 (4.0)	10 (8.1)	0.009*
Procedures: Distal gastrectomy (%)	86 (68.8)	84 (68.3)	0.931
Total gastrectomy (%)	39 (31.2)	39 (31.7)	
Lymphadenectomy: D2 (%)	3 (25.6)	28 (22.8)	
D3 (%)	93 (74.4)	95 (77.2)	0.602
Resection: R–0 (%)	83 (66.4)	88 (71.5)	
R–1 (%)	42 (33.6)	35 (28.5)	0.381
Stage I	20 (16.0)	18 (15.5)	
II	24 (19.2)	25 (21.1)	
III	48 (38.4)	47 (38.2)	
IV	33 (26.4)	31 (25.2)	0.961

* p value for location of stage III patients was 0.409.

Pathologic Examination and Classifications

All pathologic data were gathered without knowledge of the treatment category. Histologic type, TNM category, and stage were assigned using criteria provided by the Fourth Edition of the International Union Against Cancer classification; this corresponds directly to those provided in the manual of the American Joint Committee on Cancer.[31] Resections were classified as R-0 when there was a complete resection and histologic resection margins were negative. They were recorded as R-1 when the resected specimen was shown by pathologic examination to have disease at the margin of resection. Macroscopic growth variants were classified according to Borrmann types. Location of the tumor and lymph node stations were described according to the Japanese Classification of Gastric Carcinoma.[29] Examination of the specimen included evaluation of the primary tumor and separate evaluation of the lymph nodes in each station by number of lymph nodes dissected and number of positive lymph nodes. For analysis of survival, lymph node grouping (N category) was performed according to International Union Against Cancer/American Joint Committee on Cancer classifications. All 248 patients with pathologic stages I–IV were included in the final analysis.

Follow-up

All patients were followed up with regular physical examinations. A computed tomography scan and other radiologic studies along with paracentesis and laparotomy were performed at the discretion of the surgeon to confirm clinical findings. When possible, site of first recurrence, survival, and cause of death were recorded.

Statistical Analysis

The proportions of patients with a given characteristic were compared by chi square analysis or the Fisher's exact test. Differences in the means of continuous measurements were tested by the Student's t test. Survival for all discharged patients was calculated from the date of operation until death or last date of follow-up, and Kaplan-Meier survival curves were plotted and compared by the log-rank test. The differences were judged to be significant with a p value of < 0.05.

RESULTS

Patient characteristics in the study and control group are listed in Table 1. There were 125 patients in the study group and 123 in the control group. Mean duration of follow-up was 27.4 months in the study group and 25.0 months in the control group. As shown in Table 1, approximately two thirds of the patients in the study and the control group underwent distal gastrectomy, and one third in both groups underwent total gastrectomy. Also, in approximately one fourth of patients, the first and second tier (D1 and D2) of gastric lymph nodes were resected, whereas in nearly three fourths of the patients a part or all of the third and fourth tier (D3 and D4) of lymph nodes was also removed. Curiously, an analysis of cancer location in proximal stomach, body, distal stomach, or all of the stomach showed a p value of

Table 2. MORBIDITY AND MORTALITY OF PATIENTS TREATED WITH SURGERY PLUS EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY (EPIC) OR SURGERY ONLY

Morbidity/Mortality	Surgery + EPIC (%)	Surgery Only (%)	p value
Total no. of patients	125 (50.4)	123 (49.6)	
No. of patients with complications	36 (28.8)*	25 (20.3)	0.121
Anastomotic leak	4 (3.2)	3 (2.4)	1.0
Intraabdominal sepsis	17 (13.6)	5 (4.1)	0.008
Bleeding	12 (9.6)	1 (0.8)	0.002
Chyle leak	2 (1.6)	00.0	0.498
Intestinal obstruction	3 (2.4)	00.0	0.247
Wound infection	4 (3.2)	5 (4.1)	0.748
Extraabdominal complications	6 (4.8)	11 (8.9)	0.197
Relaparotomy	4 (3.2)	1 (0.8)	0.370
Percutaneous drainage	7 (5.6)	4 (3.3)	0.369
Mortality	8 (6.4)	2 (1.6)	0.102
Mean + SD days in hospital	19.6 + 11.1	15.4 + 9.5	0.002
Patients without complications	17.1 + 6.4	13.2 + 5.7	<0.001
Patients with complications	25.1 + 16.3	24.0 + 15.3	0.783

* Morbidity associated with intraperitoneal chemotherapy per se is not included.

0.009. However, the p value for location of patients with stage III disease was 0.409. None of the patients were lost to follow-up.

Morbidity and Mortality

There were eight patients in the study group who died of postoperative complications. There were two deaths in the control group (Table 2). After surgery with early postoperative intraperitoneal chemotherapy, 28.8% of patients experienced postoperative complications *versus* 20.3% in the control group. This difference was not significant but did represent a trend. There was no difference in the incidence of anastomotic leak. Conversely, there was a statistically significant increase in the incidence of intraabdominal bleeding and intraabdominal sepsis defined as abscess formation and peritonitis without anastomotic leak.

There was a number of postoperative complications unique for the patients receiving intraperitoneal chemotherapy (Table 3). Twenty-four percent of patients experienced prolonged mild-to-moderate abdominal pain upon chemotherapy instillation or drainage. Transient leukopenia occurred in 2.4% of patients. Seven percent of patients had prolonged drainage of fluid from the peritoneal cavity through drains, and 1.6% had prolonged ileus. Most of these postoperative complications can be attributed to chemotherapy-induced irritation of the peritoneal surfaces.

Table 3. MORBIDITY ASSOCIATED WITH EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

Morbidity	No. of Patients	%
Total no. of patients	125	100
No. of patients with complications	47	37.6
Pain	30	24
Prolonged drainage	9	7.2
Leukopenia (<4000/mcl)	3	2.4
Prolonged ileus (>7 days)	2	1.6
Catheter problems	2	1.6
Leak around catheter	14	11.2

Survival

Gastric resection plus early postoperative intraperitoneal chemotherapy showed improved overall survival as

Table 4. FIVE-YEAR SURVIVAL OF PATIENTS TREATED WITH SURGERY PLUS EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY (EPIC) OR SURGERY ONLY

Category	Surgery + EPIC (%)	Surgery Only (%)	p value
All stages	38.7	29.3	0.219
Curative resections (R0)	56.3	41.0	0.194
Palliative resections (R1)	13.7	0	0.249
Stage I (T2N0 only)	61.9	75.8	0.446
Stage II	39.2	53.3	0.379
Stage III	49.1	18.4	0.011
Stage IV	14.3	8.8	0.320
Stages I–III, T1-2	46.4	68.4	0.509
Stages II–III, T3-4	48.2	28.1	0.104
Stages II–III, N0	39.0	52.8	0.405
Stages II–III, N1	57.6	35.1	0.295
Stages II–III, N2	44.0	14.9	0.030

compared with surgery alone, but this was not statistically significant (Table 4). In patients with R0 and R1 resections, a 5-year survival tended to be higher after adjuvant intraperitoneal chemotherapy. When analyzed by stage, a 5-year survival showed no statistically significant improvement in patients with stage I, II, or IV disease. Only in patients with stage III disease (49.1% *vs.* 18.4%; $p = 0.011$) was there a significant improvement. In the subgroup of patients with stage III disease with metastases to the second tier of lymph nodes, the difference in 5-year survival remained pronounced (44.0% *vs.* 14.9%; $p = 0.030$). Benefits of adjuvant early postoperative intraperitoneal chemotherapy for survival were not statistically significant in subgroups of patients with invasion of the serosal surface (T3-4) and adjacent structures, but a trend was noted ($p = 0.104$). Improvement in survival was statistically insignificant for subgroups of patients with a number of metastatic lymph nodes <20% or >20% of all dissected lymph nodes ($p = 0.21$ and $p = 0.17$, respectively), and in subgroups of patients with Borrmann types 1 to 2 (expansive growth; $p = 0.14$) and Borrmann types 3 to 4 (infiltrative growth; $p = 0.25$).

Patterns of Recurrence and Causes of Death

Analysis of the pattern of failure demonstrated a trend toward decreased incidence of peritoneal dissemination after surgery with early postoperative intraperitoneal chemotherapy (9.2% *vs.* 20%) although the difference did not reach statistical significance ($p = 0.078$). A similar trend persisted when patterns of failure were analyzed by stage. There was no influence of early postoperative intraperitoneal chemotherapy on the incidence of other sites of recurrent disease. The decreased rate of all recurrences in the study group was not statistically different from that of the control group.

DISCUSSION

In a subset analysis, these data show a survival benefit in patients with stage III gastric cancer curatively resected and then treated with early postoperative intraperitoneal chemotherapy with mitomycin C and 5-fluorouracil. The 5-year survival rate was 49% in the treated group *versus* 18% in the surgery-only group ($p = 0.011$). There was no significant survival benefit in patients with stage I, II, or IV gastric cancer. Also, patients with large primary tumors but without lymph node metastases showed no significant survival benefit. In the subset analysis, it was clear that patients with lymph node metastases, especially nodal disease extending toward the lateral margins of excision, were most likely to benefit from this regional cancer treatment.

There is strong support from the literature to suggest that local failures play a prominent role in the poor survival of patients after curative resection for gastric cancer. Natural history and autopsy studies would suggest that a population of patients exists with peritoneal carcinomatosis and resection site recurrence in the absence of liver and other systemic metastases.[6–8] The results of adjuvant intraperitoneal chemotherapy trials suggest that improved locoregional control brought about by perioperative intraperitoneal chemotherapy may be successful in causing survival benefits in this group of patients.[14–17,32–34] In all published reports, survival was improved after surgery with intraperitoneal chemotherapy.[18] In two trials, survival advantage after surgery with hyperthermic intraoperative intraperitoneal chemotherapy was demonstrated in subgroups of patients with serosal invasion (T3-4 tumors) and a number of metastatic lymph nodes between 1 and 9.[15,16]

The mechanism whereby a high incidence of locoregional recurrence develops after gastrectomy has not been determined. However, this clinical study suggests that gastrectomy, especially gastrectomy with removal of regional metastatic lymph nodes, causes a dissemination of cancer in the resection bed. A local seeding of gastric cancer cells associated with the trauma of gastrectomy may be unavoidable in the resection of stage III malignancy. The success achieved with early postoperative intraperitoneal chemotherapy supports the "tumor cell entrapment" hypothesis as a mechanism of surgical treatment failure for gastric cancer.[35]

Regional chemotherapy used in the manner as in this study cannot be expected to effectively eradicate disease left behind in lymph nodes. It is likely that extended lymph node dissection is necessary for beneficial effects of perioperative chemotherapy to occur. This treatment is designed to eradicate residual microscopic disease present in the peritoneal cavity after cancer resection. Intraperitoneal chemotherapy has been demonstrated to alter the pattern of dissemination after curative surgery. Fujimura and colleagues[34] have shown in a randomized trial of hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and mitomycin C that the incidence of peritoneal spread has decreased from 22% in the control group to 9% at 3 years of follow-up. A trend toward decreased mortality from peritoneal dissemination at 5 years was noted by Hamazoe and co-workers.[17]

A collection of data published on intraperitoneal chemotherapy supports perioperative timing as an essential requirement for success.[19,20] This study used intraperitoneal chemotherapy in the early postoperative period and all prior positive randomized trials utilized intraoperative intraperitoneal chemotherapy delivery. Experimental studies have shown that residual tumor cell kinetics change within 24 hours of primary cancer removal.[36] Chemotherapy was least effective when administered 7 and more days after excision of the primary tumor.[37] Jacquet and colleagues[38] have shown that intraperitoneal chemotherapy is effective only when used within 24 hours of intraperitoneal tumor inoculation.

The survival benefit demonstrated in this study was associated with a trend toward increased morbidity and mor-

tality, although the differences were not significant. These trends were attributed to intraperitoneal chemotherapy and discussed in detail elsewhere.[39] A survival advantage in patients with stage III gastric cancer was evident despite this added mortality and suggests a robust nature of treatment effects. Our experience has shown that morbidity with perioperative intraperitoneal chemotherapy follows the pattern of a learning curve and can be reduced with experience.[39]

The survival advantage limited to patients with stage III gastric cancer and the risk of increased morbidity justify a selection of patients in future trials of perioperative intraperitoneal chemotherapy. Increasingly, sophisticated methodologies are becoming available for selection of high-risk patients. Preoperative staging methods such as endoscopic ultrasound can be useful as they become more widely available. Standard preoperative staging and careful intraoperative examination of the peritoneal cavity with biopsies performed, as needed, to verify macroscopic findings, may become a means of patient selection for perioperative intraperitoneal chemotherapy. The major selection criteria may be lymph node involvement within the second tier of lymph nodes. In patients with resectable gastric cancer, special attention must be paid to the exclusion of patients with stage I tumors for these adjuvant treatments.

References

1. Akoh JA, Macintyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publication from 1970. Br J Surg 1992: 79:293–299.
2. Hermans J, Bonenkamp JJ, Boon MC, et al. Adjuvant therapy after curative resection for gastric cancer: Meta-analysis of randomized trials. J Clin Oncol 1993: 11:1441–1447.
3. Lise M, Nitti D, Marchet A, et al. Final results of a phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin, and mitomycin regimen in resectable gastric cancer. J Clin Oncol 1995: 13(11):2757–2763.
4. Hallissey MT, Dunn JA, Ward LC, et al. The second British stomach cancer group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: Five-year follow-up. Lancet 1994: 343:1309–1312.
5. Wanebo HJ, Kennedy BJ, Chmiel J, et al. Cancer of the stomach: A patient care study by the American College of Surgeons. Ann Surg 1993: 218:583–593.
6. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: Areas of failure in a re-operation series (second or symptomatic look), clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1992: 8:1–11.
7. Wisbeck WM, Becheer EM, Russell AH. Adenocarcinoma of the stomach: Autopsy observations with therapeutic implications for the radiation oncologist. Radiother Oncol 1986: 7:13–18.
8. Landry J, Tepper JE, Wood WC, et al. Patterns of failure following curative resection of gastric carcinoma. Int J Radiat Oncol Biol Phys 1990: 1357–1362.
9. Bruckner HW, Stablein DM. Sites of treatment failure: gastrointestinal tumor study group analyses of gastric, pancreatic, and colorectal trials. Cancer Treat Symp 1983: 2:199–210.
10. Wils J, Meyer H-J, Wilke H. Current status and future directions in the treatment of localized gastric cancer. Oncology 1994: 5(Suppl 3):69–72.
11. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 1987: 11:418–425.
12. Kaibara N, Sumi K, Yonekawa M, et al. Does extensive dissection of lymph nodes improve the results of surgical treatment of gastric cancer? Am J Surg 1990: 159:218–221.
13. Korenaga D, Moriguchi S, Orita H, et al. Trends in survival rates in Japanese patients with advanced carcinoma of the stomach. Surg Gynecol Obstet 1992: 174:387–393.
14. Hagiwara A, Takahashi T, Kojima O, et al. Prophylaxis with carbon-absorbed mitomycin against peritoneal recurrence of gastric cancer. Lancet 1992: 339:629–631.
15. Yonemura Y, Ninomiya I, Kaji M, et al. Prophylaxis with intraoperative chemohyperthermia against peritoneal recurrence of serosal invasion-positive gastric cancer. World J Surg 1995: 19(1):1–6.
16. Ikeguchi M, Kondou A, Oka A, et al. Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. Eur J Surg 1995: 161:581–586.
17. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Cancer 1994: 73(8):2048–2052.
18. Sautner T, Hofbauer F, Depisch D, et al. Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. J Clin Oncol 1994: 12(5):970–974.
19. Cunliffe WJ, Sugarbaker PH. Gastrointestinal malignancy: Rationale for adjuvant therapy using early postoperative intraperitoneal chemotherapy. Br J Surg 1989: 76:1082–1090.
20. Sugarbaker PH, Graves T, DeBruijn EA, et al. Rationale for early postoperative intraperitoneal chemotherapy (EPIC) in patients with advanced gastrointestinal cancer. Cancer Res 1990: 50:5790–5794.
21. Averbach AM, Sugarbaker PH. Methodological considerations in treatment using intraperitoneal chemotherapy. In: Sugarbaker PH eds. Peritoneal Carcinomatosis: Principles of Management. Boston: Kluwer, 1996:289–310.
22. Zuka Y, Kaneshita S, Taneda O, Takeuchi T, et al. Intraperitoneal free cancer cells and their viability in gastric cancer. Cancer 1979: 44: 1476–1486.
23. Tanida O, Kaneshima S, Izuka Y, Kuda H, et al. Viability of intraperitoneal free cancer cells in patients with gastric carcinoma. Acta Cytol 1982: 26:681–687.
24. Barnes JP. Physiologic resection of the right colon. Surg Gynecol Obstet 1952: 94:401–404.
25. Fisher ER, Turnbull RB. The cytologic demonstration and significance of tumor cells in the mesenteric venous blood in patients with colorectal carcinoma. Surg Gyn Obstet 1955: 100:102–110.
26. Cole WH, Roberts SS, Webb RS, et al. Dissemination of cancer with special emphasis on vascular spread and implantation. Ann Surg 1965: 161:753–770.
27. Turnbull RB, Kyle K, Wilson FR, Spratt J. Cancer of the colon: the influence of no-touch isolation technique in survival rate. Ann Surg 1967: 166:420–427.
28. Stearns MW, Schottenfeld D. Techniques for the surgical management of colon cancer. Cancer 1971: 28:165–170.
29. Japanese Classification of Gastric Carcinoma, Japanese Research Society for Gastric Cancer. First English Edition. Tokyo:Kanehara & Co., Ltd.: 1995.
30. Yu W, Sugarbaker PH. Early postoperative intraperitoneal chemotherapy for gastric cancer. In: Sugarbaker PH ed. Management of gastric cancer. Boston: Kluwer: 1991:265–275.
31. American Joint Committee on Cancer. Manual for Staging of Cancer. Fourth Edition. Philadelphia: JB Lippincott Company: 1992.
32. Koga S, Hamazoe R, Maeta, M, et al. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. Cancer 1988: 61:232–237.

33. Shchepotin IB, Chernyi VA. Effectiveness of intraperitoneal chemotherapy in combined treatment of gastric cancer. Klinicheskaia Khirurgiia 1990: 5:7–9.
34. T, Yonemura Y, Muraoka K, et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. World J Surg 1994:18:150–155.
35. Sugarbaker PH. Peritoneal carcinomatosis: Natural history and rational therapeutic interventions using intraperitoneal chemotherapy. In: Sugarbaker PH ed. Peritoneal Carcinomatosis: Drugs and Diseases Boston: Kluwer. 1996:149–168.
36. Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor. Cancer Res 1979: 39:3861–3865.
37. Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy in kinetics and growth of metastases. Cancer Res 1983: 43:1488–1492.
38. Jacquet P, Stuart OA, Dalton R, et al. Effect of intraperitoneal chemotherapy and fibrinolytic therapy on tumor implantation in wound sites. J Surg Onc 1996: 62:128–134.
39. Yu W, Whang I, Averbach A, et al. Morbidity and mortality of early postoperative intraperitoneal chemotherapy as adjuvant therapy for gastric cancer. Am Surgeon (in press).

Discussion

DR. WALTER LAWRENCE, JR. (Richmond, Virginia): Dr. Sugarbaker, several aspects of this study are really worthy of comment.

The first comment I have is in regard to the venue for this study in a country where gastric cancer is obviously much more common than it is here. But teaming up with Dr. Yu in Taegu, you have really been able to complete a randomized clinical trial, I think something which we would find very difficult to do in this country.

But to focus now on the major thrust of your randomized trial, that of in the intraperitoneal use of chemotherapy in the perioperative period. You didn't distress the perioperative period, but I think there are data both in colon and breast cancer that suggest immediate chemotherapy may be more effective. And that an intriguing aspect of your study which can't really be addressed too well.

For a long time Dr. Sugarbaker has been working on intraperitoneal chemotherapy for established cancer. And most of us thought it was illogical and unlikely to be of any benefit, but I have to quickly say that doing it from microscopic residual is really not much different than any other adjuvant chemotherapy trials we have for systemic therapy. And there are some phase II studies that have suggested what you have done today are going to work. The one at the University of Southern California Cancer Center has a phase II trial which seems to show benefit. But theirs is confused by systematic as well as intraperitoneal and yours has that advantage. I might say that most of us skeptics though would have to say that you need a larger trial and a repeat trial with several things addressed before some of us can really accept this as the state of art.

First of all, subset analyses after the fact are sort of hard to swallow. And I am sure that you feel the same way. You only found this in one area. The other thing is that we found, as many will you will remember the small GI tumor adjuvant trial showed exciting benefit from 5 FU and Methyl CCNU systemically and yet when we had a bigger VA trial later there was absolutely no difference. So several questions I would like to ask.

One, in the manuscript you mention that the median follow-up time is about 2 years and yet a lot of your data are for 5-year survival. I am a little confused by that and wondering even whether or not maybe you have hurt yourself some in 5-year survivals by having short follow-up.

You are obviously going to continue these studies in terms of trying to get—and you have a broad spectrum of stages, when you really wanted to study only stages II and III. Would it be possible to use endoscopic ultrasound, possibly endoscopic ultrasound with fine needle aspiration biopsy of regional nodes, like we are now doing, to better at least stratify these cases, if not limit the cases that might be appropriately studied.

And lastly, I wondered whether you would consider in subsequent trials doing something like was done in the NSABP portal vein colon cancer trial, having the control group be a little more like the treatment group, in other words having intraperitoneal wash of some placebo solution with the same catheters rather than no treatment at all. I think we are all indebted to you for bringing a very interesting set of ideas to us and I am sure there are many other trials in the future that are going to be pursued because of this study.

DR. PAUL H. SUGARBAKER (Washington, D.C.): The statistics here, Dr. Lawrence, are quite routine. The Kaplan-Meier survival curve and the log-rank test are used to determine 5-year survivals. Yes, I would like to see follow-up prolonged. Of course we will look at this again in the future. With additional follow-up we might do better in terms of the statistics, realizing that there were six additional deaths in the study group related to treatment, and perhaps with time that negative effect will diminish. As far as using endoscopic ultrasound, it was not available in Taegu. Neither is it available currently at my institution. I agree that it is something that may be of benefit. However, I like the way we did this trial. In order to eliminate noise from the system, we performed the randomization intraoperatively after the gastrectomy. I know statisticians have repeatedly criticized this approach. Had we performed the randomization preoperatively, I don't think we would have had any statistically relevant data at all. Now, what would be the arms of the next trial where early postoperative intraperitoneal chemotherapy is the accepted state-of-the art control. For example, what would that trial look like if it were put into the German clinical trials machine that we just saw demonstrated or into the Dutch clinical trials machine. I think I would suggest the simplest two-armed study, which would be surgery only *versus* surgery plus an intraoperative chemotherapy wash. The intraoperative chemotherapy would treat the entire abdomen and pelvis prior to rather than after the creation of intestinal anastomoses.

DR. HAROLD J. WANEBO (Providence, Rhode Island): The use of intraperitoneal chemotherapy for microscopic disease has been piloted by Dr. Sugarbaker and by the Japanese in many different trials, and it has shown some benefit.

This case focuses on two concepts. One concept is the timing, that is the intraoperative positioning of catheters in the immediate treatment of those patients so it is truly perioperative, and the route, which is also the old Willie Sutton approach to cancer, that is to go right where the disease is. And he certainly has done that.

Dr. Sugarbaker, you do have increased complications, sepsis, bleeding, and even an increase in mortality, although it is not statistically significant in the treated group. Is this avoidable? Is there some purely technical issue? Was it truly drug toxicity? Is there something that could be done about this so that you could broaden your trial? Secondly, there is a somewhat disturbing decrease in survival in some subgroups, *i.e.* stage I and II in the